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A simple screening method for the diagnosis of chronic myeloid leukemia using the parameters of a complete blood count and differentials

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ABSTRACT

Background: This study aimed to develop a simple and inexpensive method using the complete blood count (CBC) and differentials to screen for chronic myeloid leukemia (CML).
Methods: The receiver operating characteristic (ROC) curves of each CBC parameter, differential and the neutrophil alkaline phosphatase (NAP) score using CML and non-CML cases were generated to determine effective cut-off values. They were applied to the review of randomly-selected 45,608 samples for validation.
Results: The leukocyte count showed the highest area under the ROC curve (AUC) value (0.909) among the CBC parameters. In the absolute counts of differentials, the AUC was the highest in basophils (0.982), followed by immature granulocytes (IGs) (0.975), which had cut-off values of 0.43×10^9/L and 0.46×10^9/L, respectively. The AUC of the NAP score was 0.963 at a cut-off value 122. In the validation, the absolute basophil counts were elevated in 280 samples from 96 cases, including 22 CML cases. In contrast, the absolute IG counts were elevated in 1310 samples from 516 cases, including only 17 CML cases. Three newly-diagnosed CML cases whose data were analyzed sequentially at the CML onset consistently met the basophil criteria before the IG criteria.
Conclusions: The absolute basophil count is effective for screening for CML.

1. Introduction

Chronic myeloid leukemia (CML) is genetically characterized by the formation of chromosomal translocation t(9;22) (q34;q11.2), which generates the hallmark fusion gene *BCR-ABL1* [1]. As the resultant product possesses tyrosine-kinase domains, several tyrosine kinase inhibitors (TKIs) targeting these domains have been developed and have become the standard therapy for CML. The two-year progression-free survival and overall survival with imatinib, a first-generation TKI, to CML in chronic phase (CML-CP) have been reported as 88–98% and 95–100%, respectively [2,3]. The administration of second-generation TKIs, such as nilotinib and dasatinib, has been shown to provide even faster and deeper molecular responses than a first-generation TKI imatinib, resulting in the further improvement of the outcomes of CML patients [3–5]. On the other hand, chemotherapy with TKIs and allogeneic hematopoietic stem cell transplantation (allo-HSCT) are still required in patients with CML in the advanced stage, such as accelerated phase (AP) and blastic crisis (BC) [6–8]. It is therefore desirable for patients to be diagnosed at an early stage in order to receive less-intense therapy and obtain a better prognosis.

The diagnosis of CML requires the detection of *BCR-ABL1* [1], which is usually accomplished by reverse transcription-polymerase chain reaction (RT-PCR) and fluorescence *in situ* hybridization (FISH). However, patients with CML are usually asymptomatic unless they are in an advanced stage or have huge splenomegaly. A blood test including a complete blood count (CBC) and differentials is a valuable opportunity to screen for CML at an early stage, as people undergo routine blood tests for a variety of reasons other than CML.

The purpose of this study was to develop a simple, inexpensive method of screening routine blood tests to extract cases with CML at an

Abbreviations: AUC, area under the receiver operating characteristic (ROC) curve; CBC, complete blood count; CML, chronic myeloid leukemia; CP, chronic phase; IG, immature granulocyte; MPN, myeloproliferative neoplasms; NAP, neutrophil alkaline phosphatase; ROC, receiver operating characteristic; TKI, tyrosine kinase inhibitor

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Table 1
Area-under-the-curve values for the parameters for chronic myeloid leukemia screening.

	CML	†Non-CML	*p*-value	cut-off level	AUC
A. Complete blood count parameters					
Number of cases	115 (CP:111 AP:4)	520			
Age (years)	53 (19–89)	65 (20–93)	< 0.001	NA	NA
Sex (M/F)	78/37	285/235	0.012	NA	NA
White blood cell count ($x10^9$/L)	38.0 (6.0–435.3)	12.3 (8.1–113.5)	< 0.001	21.0	0.909
Red blood cell count ($x10^{12}$/L)	4.37 (2.24–5.60)	4.10 (1.40–8.97)	0.003	4.20	0.583
Hemoglobin (g/dL)	13.2 (6.8–16.6)	12.3 (4.3–21.0)	0.066	13.1	0.568
Hematocrit (%)	40.9 (21.0–49.3)	38.1 (15.9–64.0)	0.095	40.6	0.558
Platelet count ($\times 10^9$/L)	487 (93–2395)	251 (1–2654)	< 0.001	326.0	0.744
Differentiation (%)					
Blasts	0.5 (0.0–9.5)	0.0 (0.0–8.0)	< 0.001	0.3	0.773
Promyelocytes	0.00 (0.0–4.0)	0.0 (0.0–1.0)	< 0.001	0.3	0.629
Myelocytes	11.5 (0.0–34.5)	0.0 (0.0–32.5)	< 0.001	1.8	0.964
Metamyelocytes	3.0 (0.0–15.0)	0.0 (0.0–10.0)	< 0.001	0.3	0.934
Segmented and stab neutrophils	63.0 (37.5–85.0)	76.6 (2.0–98.5)	< 0.001	NA	0.271
Eosinophils	2.5 (0.0–10.0)	1.0 (0.0–66.5)	< 0.001	1.5	0.696
Basophils	5.5 (0.0–37.0)	0.4 (0.0–7.0)	< 0.001	1.9	0.965
Monocytes	2.5 (0.0–35.0)	4.5 (0.0–37.0)	< 0.001	NA	0.271
Lymphocytes	7.5 (0.5–38.0)	14.0 (0.0–96.0)	< 0.001	NA	0.281
Immature granulocytes (Myelo + Meta)	16.5 (0.0–46.5)	0.0 (0.0–36.5)	< 0.001	1.8	0.970
Absolute blood cell count ($\times 10^9$/L)					
Blasts	0.16(0.00–14.33)	0.00(0.00–2.55)	< 0.001	0.02	0.780
Promyelocytes	0.00(0.00–17.41)	0.00(0.00–0.15)	< 0.001	0.18	0.629
Myelocytes	4.53(0.00–117.02)	0.00(0.00–15.30)	< 0.001	0.37	0.967
Metamyelocytes	1.26(0.0–60.94)	0.00(0.00–5.36)	< 0.001	0.07	0.941
Segmented and stab neutrophils	25.36(3.06–213.30)	8.44(1.09–65.70)	< 0.001	14.09	0.869
Eosinophils	1.06(0.00–18.38)	0.12(0.0–17.22)	< 0.001	0.37	0.891
Basophils	2.46 (0.00–25.85)	0.04 (0.00–2.68)	< 0.001	0.43	0.982
Monocytes	1.02(0.0–40.88)	0.59(0.00–13.19)	< 0.001	0.80	0.685
Lymphocytes	2.88(0.62–17.41)	1.75(0.00–108.96)	< 0.001	2.30	0.717
Immature granulocytes (Myelo + Meta)	5.80 (0.00–168.22)	0.0 (0.00–306.08)	< 0.001	0.46	0.975
B. NAP score					
Number of cases	106 (CP:106)	161			
Median age (years)	53 (19–89)	68 (11–95)	< 0.001	NA	NA
Sex (M/F)	74/33	91/70	0.041	NA	NA
NAP score	67 (10–214)	274 (9–484)	< 0.001	122	0.963

Values are expressed as the median with the range in parentheses unless otherwise indicated.
AP, accerelated phase; CML, chronic myeloid leukemia; CP, chronic phase; NA, not applicable; NAP, neutrophil alkaline phosphatase; Myelo, myelocytes; Meta, metamyelocytes.
† Non-CML includes cases with leukocytosis (leukocytes $\geq 8.0 \times 10^9$/L) in A as well as cases with erythrocytosis (hemoglobin level ≥ 16.0 g/dL, or hematocrit ≥ 48.0%), thrombocytosis (platelets $\geq 450 \times 10^9$/L) or leukocytosis (leukocytes $\geq 8.0 \times 10^9$/L) in B.

early stage.

2. Patients and methods

2.1. Patients

One hundred and fifteen newly diagnosed CML cases between June 2004 and January 2016 in Tokai University Hospital were examined in this study. Their CBC and differential data were compared with those from 520 adult outpatient cases with non-CML leukocytosis (white blood cell $\geq 8.0 \times 10^9$/L) analyzed in January 2016. To assess the utility of the neutrophil alkaline phosphatase (NAP) score, 106 of the 115 CML cases and 161 non-CML cases evaluated for myeloproliferation (meeting 1 of the following criteria: leukocytes, $\geq 8.0 \times 10^9$/L; hemoglobin level, ≥16.0 g/dL; hematocrit, ≥48.0%; platelets, $\geq 450 \times 10^9$/L) between April 2000 and December 2015 were compared. Their backgrounds are shown in Table 1. The randomly selected 45,608 CBCs with differential counts measured in our clinical laboratory between April 2015 and March 2016 were reviewed in the subsequent validation analysis.

All of these studies were performed in accordance with the Declaration of Helsinki and with approval from the Institutional Review Board for Clinical Research of Tokai University (Permit number: 16R019).

2.2. Analyses of peripheral blood parameters and the NAP score in each case

The CBCs and differentials were determined using automated hematology analyzers XE-2100 (through April 2013) or XN-3000 (from May 2013) (Sysmex Corporation, Kobe, Japan). The absolute counts of differentials were calculated using the absolute leukocyte count and their frequency in the peripheral blood. The NAP score was evaluated based on Tomonaga's method using an ALP staining kit (Muto Pure Chemicals, Tokyo, Japan).

2.3. Statistical analyses

The normality of the data was analyzed by the Kolmogorov-Smirnov test. Parametric and Non-parametric data were analyzed a by *t*-test and the Mann–Whitney *U* test, respectively. The relationship between sex and disease type was analyzed using Fisher's exact test. *P* values of < 0.05 were considered to indicate statistical significance.

The receiver operating characteristic (ROC) curves for each parameter were plotted. The nearest point to the top-left corner of the plot, which provided 100% sensitivity and a 0% false positive rate, was determined as the cut-off value.

All of the statistical analyses were performed using the SPSS statistics software program, ver. 23 (IBM).

3. Results

3.1. Analyses of peripheral blood parameters

To identify the most effective parameters in routine blood tests for screening CML, the CBCs and the absolute counts of differentials in 115 CML cases and 520 non-CML leukocytosis cases were compared (Table 1). The CML cases were younger and more often male than the non-CML leukocytosis cases.

All the parameters in routine blood tests showed statistical significance ($p < 0.05$), with the exception of the hemoglobin concentration and hematocrit. The ROC curves of each peripheral blood parameter were generated, and their areas under the ROC curve (AUC) were measured. The leukocyte count showed the highest AUC value (0.909) among the CBC parameters at a cut-off value of 21.0×10^9/L. In order to identify a specific differential in the leukocytes, an analysis was performed for each leukocyte differential. The AUC values of basophils, myelocytes and metamyelocytes were all > 0.9 (0.965, 0.964 and 0.934, respectively), and their cut-off values were 1.9%, 1.8% and 0.3%, respectively. Because of the morphological similarity of myelocytes and metamyelocytes, their combination (immature granulocytes [IGs]) was also analyzed. The AUC value was 0.970, which was higher than that of basophils, at a cut-off value of 1.8%. In contrast, the AUC value of eosinophils, which are known to proliferate in various myeloproliferative neoplasms, was 0.696.

Then the absolute counts of each differential, which were calculated by multiplying each leukocyte differential by the leukocyte count, were applied to the analysis. The basophils showed the highest AUC value (0.982) among all of the differentials at a cut-off value 0.43×10^9/L. The second- and third-highest AUC values were obtained from the analyses using the absolute myelocyte and metamyelocyte counts: 0.967 at a cut-off value 0.37×10^9/L and 0.941 at a cut-off value 0.07×10^9/L, respectively. When myelocytes and metamyelocytes were combined as IGs, the AUC value increased to 0.975 at a cut-off value 0.46×10^9/L.

Because the absolute counts of basophils and IGs provided the highest and second-highest AUC values among all of the differential counts and their absolute counts, these two parameters were used to evaluate the screening ability of annual CBC data obtained at our hospital.

3.2. Analyses of the NAP score

The NAP score test is not usually included in the routine blood test but is often performed for CML cases as an additional examination. Therefore, the utility of NAP score test for screening CML was evaluated. The NAP score test results from 106 CML cases and 161 non-CML cases for the evaluation of myeloproliferation were compared. The AUC value was 0.963 at a cut-off value of 122, which was comparable with those of the absolute basophil and IG counts (Table 1).

3.3. Sensitivity and specificity of the candidate parameters

The sensitivity and specificity of the absolute basophil and IG counts were analyzed (Table 2). Their sensitivities were identically 93.9%, but the specificity was higher in the absolute basophil count (95.2%) than in the absolute IG count (93.7%). There were 25 and 33 false-positive cases in the analysis using the absolute basophil and IG counts, including 24 and 11 cases with non-CML myeloproliferative neoplasms (MPN), respectively.

If the cases that satisfied either of the basophil or IG cut-off values were analyzed, the sensitivity increased to 99.1%, but the specificity decreased to 90.2% due to the increased number of false-positive cases. When the cases that satisfied both the basophil and IG cut-off values were analyzed, the specificity increased to 98.7% but the sensitivity decreased to 88.7%.

The sensitivity and specificity of the NAP score test were 95.3% and 90.7%, respectively (Table 2). There were 15 false-positive cases, including 11 non-CML MPN and 4 myelodysplastic/myeloproliferative neoplasms (MDS/MPN). Although the NAP score tests were not performed at regular blood checkups, the results were comparable with those of the absolute basophil and IG counts.

3.4. The usefulness of absolute basophil counts for screening CML

Because CBCs but not the NAP score test are commonly performed as a fundamental examination, the absolute basophil and IG counts and their combination were deemed candidate simple tests for screening CML. Randomly selected CBC samples with differentials were retrospectively screened for their validation (Table 3).

Of the 45,608 samples, 280 samples (0.61%) from 96 cases were revealed to have elevated absolute basophil counts of $\geq 0.43 \times 10^9$/L. These 96 cases included 22 CML cases, which included 15 newly diagnosed cases. The remaining 74 cases (77.1% of the 96 positive cases) were false-positive and non-CML. If the IG cut-off value was applied to the 74 false-positive cases, only 39 cases (52.7% of the 74 false-positive cases) were ruled out based on a low IG count of $< 0.46 \times 10^9$/L. Regarding the NAP score, the test was performed in 42 of the 74 false-positive cases, and effectively ruled out 36 cases (85.7% of the 42 cases) with a high NAP score.

When an absolute IG count of $\geq 0.46 \times 10^9$/L was utilized for the initial screening of CML, 1310 samples (2.87% of the total 45,608 samples) from 516 cases were positive. However, only 17 cases were actually CML, resulting in a lot of false-positive non-CML cases (499 cases, 96.7% of all 516 positive cases). If the basophil cut-off value was applied to these 499 false-positive cases, most (495 cases, 99.2% of the 499 false-positive cases) were ruled out by decreased absolute basophil counts. The NAP score test was performed in 45 out of the 499 false-positive cases, but it was not useful; Only 26 cases (57.8% of 45 cases) were ruled out based on a high NAP score.

A total of 1477 samples (3.24% of the total 45,608 samples) from 567 cases satisfied either of the basophil or IG cut-off values described above. These included all 22 CML cases who were detected using the basophil cut-off value alone, but there were lots of false-positive non-CML cases (545 cases, 96.1% of all the 567 positive cases).

Conversely, 113 samples (0.25% of the total 45,608 samples) from 35 cases satisfied both of the basophil and IG cut-off values. The frequency of false-positive cases was relatively low (51.4%, 18 cases out of the 35 positive cases); however, these included only 17 CML cases.

Taken together, these data show that an elevated absolute basophil count with a cut-off value of 0.43×10^9/L is a suitable predictive factor for screening CML. In addition, a decreased NAP score (cut-off value: 122) might be helpful for excluding false-positive cases in combination with the basophil cut-off values, if the test is performed.

3.5. Sequential changes in the leukocyte differentials around the onset of CML

The basophil criteria extracted the three cases that had attended our hospital due to non-hematological diseases. They were newly diagnosed with CML during their follow-up (Table 4). The sequential data of their CBC and differentials allowed us to observe the initial changes at the onset of CML (Fig. 1). In all 3 of these cases, leukocytosis progressed with the increase in the basophils and IGs, and the increase in basophils always preceded that in IGs.

These findings may suggest the close correlation between the development of CML and the proliferation of basophils.

4. Discussion

The findings presented in this study clarified the absolute basophil count ($\geq 0.43 \times 10^9$/L) that provided the highest AUC value with high

Table 2
The sensitivity and specificity of the absolute basophil and immature granulocyte counts and NAP score.

A. Complete blood count parameters	CML (n = 115)		†Non-CML (n = 520)		Sensitivity (%)	Specificity (%)
	Positive	Negative	Positive	Negative		
a. Absolute basophil count ($\geq 0.43 \times 10^9$/L)	108	7	25	495	93.9	95.2
b. Absolute immature granulocyte count ($\geq 0.46 \times 10^9$/L)	108	7	33	487	93.9	93.7
c. a or b	114	1	51	469	99.1	90.2
d. Both a and b	102	13	7	513	88.7	98.7

B. NAP score	CML (n = 106)		non-CML (n = 161)		Sensitivity (%)	Specificity (%)
	Positive	Negative	Positive	Negative		
≤122	101	5	15	146	95.3	90.7

CML, chronic myeloid leukemia; NAP, neutrophil alkaline phosphatase.
† Non-CML includes cases with includes cases with leukocytosis (leukocytes $\geq 8.0 \times 10^9$/L) in A as well as cases with erythrocytosis (hemoglobin level ≥ 16.0 g/dL, or hematocrit ≥48.0%), thrombocytosis (platelets $\geq 450 \times 10^9$/L) or leukocytosis (leukocytes $\geq 8.0 \times 10^9$/L) in B.

Table 3
The utility of the absolute basophil and immature granulocyte counts for chronic myeloid leukemia screening.

Parameters	Number of total positive samples (frequency in 45,608 samples)	Number of total positive cases	Number of CML cases (newly-diagnosed)	Number of non-CML cases (frequency in total positive cases)
a. Absolute basophil count ($\geq 0.43 \times 10^9$/L)	280 (0.61%)	96	22 (15)	74 (77.1%)
b. Absolute immature granulocyte count ($\geq 0.46 \times 10^9$/L)	1310 (2.87%)	516	17 (11)	499 (96.7%)
c. a or b	1477 (3.24%)	567	22 (15)	545 (96.1%)
d. Both a and b	113 (0.25%)	35	17 (11)	18 (51.4%)

CML, chronic myeloid leukemia.

Table 4
The characterization of three newly diagnosed CML cases followed up due to other diseases.

	Case 1	Case 2	Case 3
Age (years)/Sex	40s/M	60s/F	30s/M
Primary disease	Liver chirrhosis	Atrial fibrillation	IgA nephropathy
Leukocytes ($\times 10^9$/L)	11.6	14.8	7.3
Hemoglobin (g/dL)	13.9	13.2	15.5
Platelets ($\times 10^9$/L)	167	659	810
Blasts (%)	0.0	0.0	0.0
Absolute basophil counts ($\times 10^9$/L)	1.45	0.81	0.56
Absolute immature granulocytes ($\times 10^9$/L)	0.35	0.30	0.37
Sokal score	1.02 (Intermediate risk)	1.19 (Intermediate risk)	0.93 Intermediate risk)
Hasford score	1152 (Intermediate risk)	1279 (Intermediate risk)	839 (Intermediate risk)
EUTOS score	146.3 (High risk)	71.5 (Low risk)	96.8 (High risk)

sensitivity and selectivity for screening CML. When this criterion was used to survey 45,608 CBC routine laboratory samples for validation, the absolute basophil counts were elevated in 280 samples (0.61%) from 96 cases, including 22 cases with CML (15 newly diagnosed cases).

Basophilia is a characteristic feature of CML but is also caused by several medical conditions, including myeloproliferative neoplasms other than CML, hypothyroidism, chronic allergic and inflammatory reactions [9]. Masuda et al. reported that the absolute basophil counts were significantly higher in CML than in non-CML disorders and that non-CML cases with absolute basophil counts exceeding 0.50×10^9/L were quite rare [10]. Ogunleye et al. extracted CML cases from a review of PCR orders for *BCR-ABL1* using a cut-off level of 0.1×10^9/L for the absolute basophil count, but the population was small [11]. In our study, cases of non-CML leukocytosis rather than randomly selected adult non-CML cases were employed as references. Relatively severe basophilia (up to 2.68×10^9/L) was recognized in some non-CML leukocytosis cases in this study, but there were still significant differences between the CML and non-CML leukocytosis cases with a cut-off level of 0.43×10^9/L, which was even lower than that previously reported in Masuda's study [10].

The absolute IG count, including myelocytes and metamyelocytes, was another candidate predictive factor for screening CML from the perspective of simplicity, sensitivity and specificity. Myelocytes and metamyelocytes generated high AUC values individually and even higher ones when they were combined as IGs. In Masuda's study, the absolute counts of myelocytes but not metamyelocytes provided a high AUC value [10]. Myelocytes and metamyelocytes are usually discriminated by their morphological features on a smear, but this can be difficult. It is therefore reasonable to combine them as a single predictive factor for screening CML, as seen in our study. We extracted about five times more cases based on the absolute IG counts in the validation study than the absolute basophil count, but > 95% of them were false-positive for CML. This is because IGs also appear in other myeloid neoplasms and are not specific for CML. Therefore, the absolute IG count was found to be less effective for screening than the absolute basophil count alone.

The NAP score test was also shown to have good sensitivity and selectivity comparable to the absolute basophil and IG counts. However, it is not usually performed as a routine test and is accordingly deemed unsuitable for primary screening of CML. The NAP score test was actually helpful for screening false-positive cases extracted by the absolute basophil counts in our study. However, MPN cases with *Calreticulin* gene mutations, which are detected in 20% to 30% of essential thrombocytosis and primary myelofibrosis cases [12,13], have been reported to show a low NAP score [14]. Therefore, the ability of the NAP score test to screen CML might be limited.

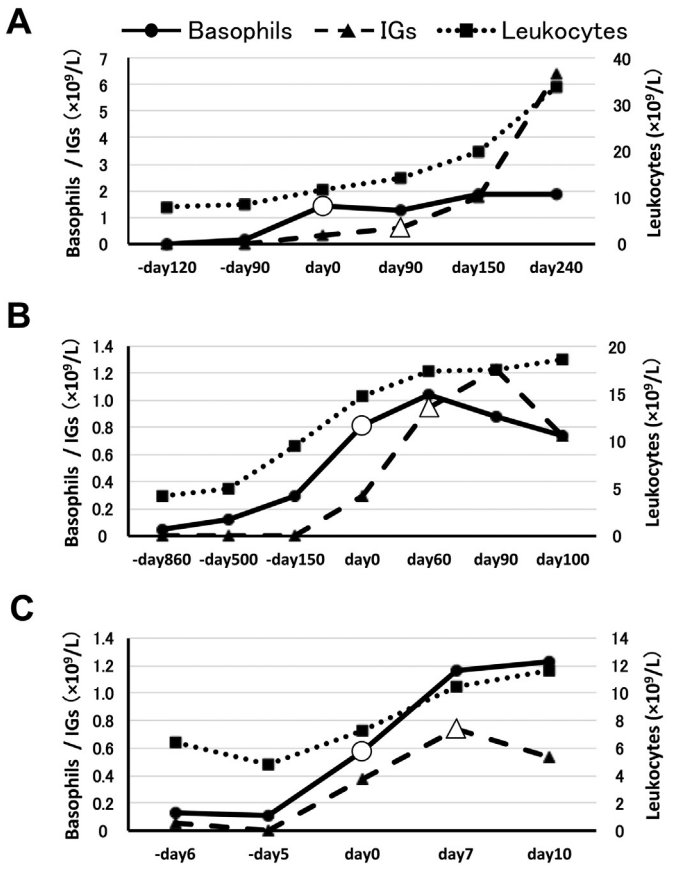

Fig. 1. Sequential changes in leukocyte differentials around the onset of CML. The changes in the counts of leukocytes and absolute basophils and immature granulocytes (IGs, myelocytes plus metamyelocytes) in the three newly diagnosed CML cases that had attended our hospital due to non-hematological diseases are presented. Day 0 means the first day at which the absolute basophil counts were ≥ 0.43×10^9/L (open circles). The open triangles indicate the first point when the absolute IG counts were ≥ 0.46×10^9/L.

An interesting finding in our study was that the increased basophil count preceded the IG increase in all three newly diagnosed CML cases, suggesting that basophils predominantly develop and proliferate even at the initial stage of CML. Basophilia worsens as the disease progresses, according to the criteria for accelerated phase in WHO classification [1]. In addition, basophilia was an independent prognostic factor of CML before the TKI era [15–18]. Functionally, BCR-ABL1 has been reported to induce the expression of histidine decarboxylase (HDC), which synthesizes histamine, thereby mediating basophil development [19–21]. Taken together, these findings including ours emphasize the close relationship between the development of CML and basophilia.

The incidence of CML has been estimated at 1 to 2 cases per 100,000 people [1], which is not as high as in other common cancer types. CBCs and differential tests are often performed during health checkups and medical examinations to detect general hematological problems. The criteria using the absolute basophil count obtained in our study can help to identify CML-suspected patients among the total population who undergo the CBC and differential tests. It may lead to the diagnosis of CML at an earlier stage, resulting in an improved prognosis with conventional TKIs, instead of more complicated therapies, including allo-HSCT. This screening may also be cost-effective by reducing the number of cases with allo-HSCT [22–25]; however, further study is required to prove this effect.

In conclusion, an absolute basophil count of ≥0.43×10^9/L is a simple, cost-effective, easily applicable marker for screening CML cases at an early stage.

Conflict of interest statement

The authors declare no conflicts of interest in association with the present study.

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